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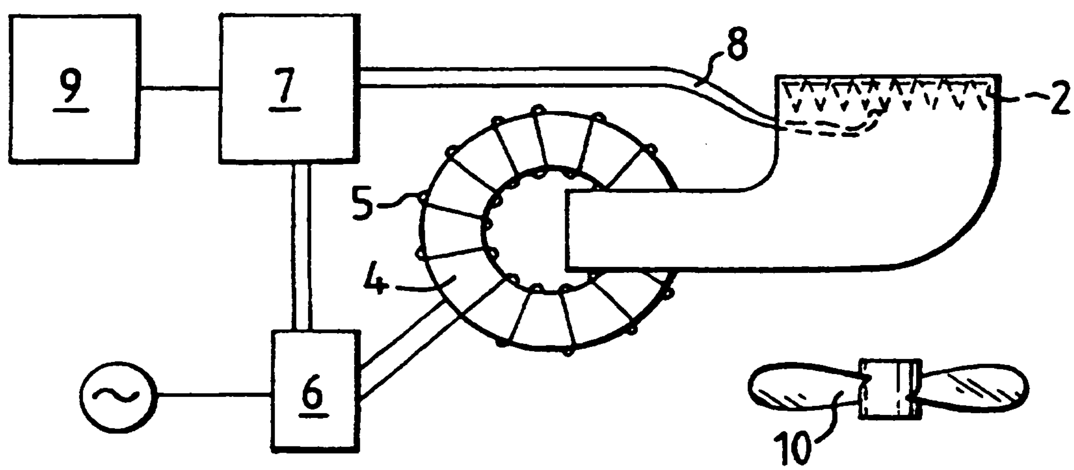
(54) Title: HEATING



(57) Abstract

A method and apparatus for heating specimens in wells of a metallic specimen carrier. The specimen carrier is heated by applying resistive heating directly to the carrier. An AC source and transformer may be used where the specimen carrier is in series with a single turn secondary winding of the transformer.

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"**Heating**"

The present invention relates to heating and more particularly to the thermal cycling of specimen carriers.

In many fields specimen carriers in the form of support blocks or platterns are used for various processes where small samples are thermally cycled.

A particular example is the Polymerase Chain Reaction method (often referred to as PCR) for replicating DNA samples. Such samples require rapid and accurate thermal cycling, and are typically placed in a multi-well block and cycled between several selected temperatures in a pre-set repeated cycle.

Previous methods of heating such specimen carriers have involved use of resistance wire coiled around the wells, use of Peltier effect devices or hot air methods. However such methods are difficult to control to the precision required, necessitate slow cycle times and can give rise to thermal over shoot.

The present invention solves this problem by applying direct electrical resistive heating to a metallic specimen carrier. Thus the invention provides a method of heating a specimen carrier in the form of a metallic

sheet and applying a heating current to said sheet.

Preferably the metallic sheet will be of silver which has a high thermal and electrical conductivity. The sheet will generally have a thin section in the region of 0.3mm thickness, and may be in a form where a matrix of sample wells is incorporated in the sheet.

While the metallic sheet may be a solid sheet or block of silver (which may have cavities forming wells) an alternative is to use a metallised plastic tray (which may have impressed wells), in which deposited metal forms a resistive heating element.

Another alternative is to electro form a thin metal tray (which again may have impressed wells), and to coat the metal with a bio-compatible polymer.

These measures enable intimate contact to be achieved between the metallic heating element and the bio-compatible sample receptacles. This gives greatly improved thermal performance in terms of temperature control and rate of change of temperature when the actual temperatures of the reagents in the wells is measured.

The plastic trays are conventionally single use

disposable items. The incorporation of the heating element into the plastic trays may increase their cost, but the reduction in cycling time for the PCR reaction more than compensates for any increased cost of the disposable item.

The bottom of the composite tray should be unobstructed when fan cooling is employed. If sub-ambient cooling is required at the end of the PCR cycles, either with a composite tray or a block, chilled liquid spray-cooling may be employed. The boiling point of the liquid should be below the low point of the PCR cycle so that liquid does not remain on the metal of the tray or block to impede heating. This also allows for the latent heat of evaporation of the liquid to increase the cooling effect.

The heating current may be an AC current supplied from the secondary winding of a transformer. This allows cycling control to be applied to the primary circuit of the transformer (higher voltage, lower current) in a convenient way without encountering problems which arise when operating with high current devices.

The transformer may comprise a toroidal core having an appropriate mains primary winding and a single bus bar looped through the core and connected in series with the

metallic sheet to form a single turn secondary circuit.

An embodiment of the invention will now be described by way of example with reference to the accompanying diagrammatic drawings in which:

Figure 1 is a side elevation of a heating apparatus, and

Figure 2 is a plan view of the apparatus of Figure 1.

A metallic specimen carrier in the form of a multi-well block (1) measuring 110mm x 75mm and having 96 wells (2) disposed in a grid layout is formed in silver nominally 0.3mm thick. This is attached to bus bars (3) of substantial cross-sectional area. The bus bars loop once through a transformer (toroidal or square), core (4). The core (4) has a primary winding (5) appropriate for the mains voltage employed. The transformer primary current is controlled using a triac device (6). The triac device receives current from an AC source and is controlled by a temperature control circuit (7) which uses a fine wire thermocouple (8) soldered to a central underside region of the block to sense the temperature of the block. The temperature control circuitry may be operated manually or by a personal computer (9).

Cooling of the block is by means of a fan (10) mounted under the block, blowing ambient air over the protruding well forms (2), the air being directed by the enclosure in which the block is mounted. The fan is controlled by the same temperature control circuitry that drives the heater triac.

The measured performance of the example apparatus gives rates of change of temperature in excess of 6 degrees per second and over/under shoots of less than 0.25 degrees within the typical PCR working range of 50-100 degrees.

The described examples use a silver block with cavities, but metalised plastic tray inserts, or electro formed thin metal trays, as previously described, may also be used.

The system as described has several important advantages.

1.1 The block is heated directly with no requirement for heat transfer from an attached heat source. This is very efficient and taken together with the very low specific heat capacity of silver allows very rapid temperature changes.

1.2 Direct heating means that there is no thermal lag at all. Temperature control functions are immediate

so that the block may be cycled in temperature with little or no over or undershoot. Temperature control is therefore inherently precise.

1.3 Since there are no obstructions or thermal barriers attached to the block, simple forced-air cooling of the back of the block (which may be shaped to increase its surface area), provides rapid and controllable cooling.

1.4 The fine wire thermocouple is soldered directly to the block so as to provide close temperature measurement and control. Any other temperature measurement device may be used as long as it does not introduce significant sensor lag.

1.5 The temperature distribution around the surface of the block is dependent on the evenness of heating and the thermal conductivity of the block. The thermal conductivity of silver is very high, and the distribution of heat energy around the block is dependent upon the distribution of the heating current. This may be regulated by varying the geometry of the multi-well block.

The large currents required may be easily produced and

controlled since the block becomes part of a heavy secondary circuit of the transformer. The cross-sectional area of the winding bars is made considerably larger than the cross-sectional area of the block so that significant heat generation only occurs in the block. The current can be easily controlled in the primary winding (where the current is small), using thyristors, triacs or other devices. Alternatively, the primary winding may be driven by a high frequency, switch mode, controllable power supply. This allows the same degree of control of the current induced in the secondary winding incorporating the block, but the high frequency allows the use of a more compact core in the transformer, and reduces inrush current surges when switching the current on and off.

CLAIMS:

1. A method of heating a specimen carrier of the kind comprising a plurality of specimen sites such as wells, which carrier is in the form of a metallic sheet and the method comprising applying a current to said sheet so as to provide resistive heating of said sheet so as to heat specimens carried by said carrier.

2. A method according to Claim 1 in which the heating is applied as an alternating current providing resistive heating, and is controlled to provide repeated cycles of heating.

3. A method according to any preceding claim in which said metallic sheet is a solid block of silver.

4. A method according to any preceding claim in which said sheet is a metallised plastic tray.

5. A method according to any preceding claim in which said sheet is an electro-formed thin metal tray.

6. A method according to any preceding claim in which said metallic sheet includes a plurality of wells to contain a plurality of specimens.

7. Apparatus for carrying out the method of any preceding claim comprising a specimen carrier of the kind carrying a plurality of specimen sites such as wells, which carrier is in the form of a metallic electrically conductive sheet, power supply means, and a transformer having a primary winding connected to said power supply means, and a secondary winding directly connected to said conductive sheet.

8. Apparatus according to claim 7 in which said secondary winding is a single turn winding.

9. Apparatus according to any of Claims 7 or 8, comprising temperature control means connected to regulate flow of heating current through said secondary winding at a rate which maintains a controlled heating temperature within said specimen carrier.

10. Apparatus according to Claim 9 comprises fan cooling means arranged to direct cooling air to a rear side of said specimen carrier and operatively connected to said temperature control means.

11. Apparatus according to any of Claims 7 to 10 in which said metallic sheet is a solid block of silver.

12. Apparatus according to any of Claims 7 to 10 in which said metallic sheet is a metallised plastic tray.

13. Apparatus according to any of Claims 7 to 10 in which said metallic sheet is an electro-formed thin metal tray.

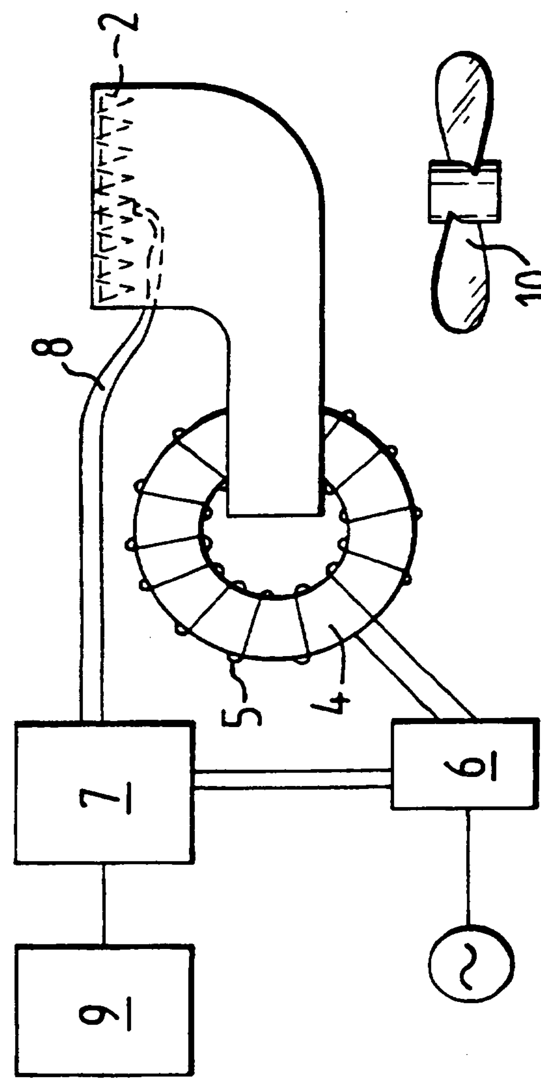

FIG.1

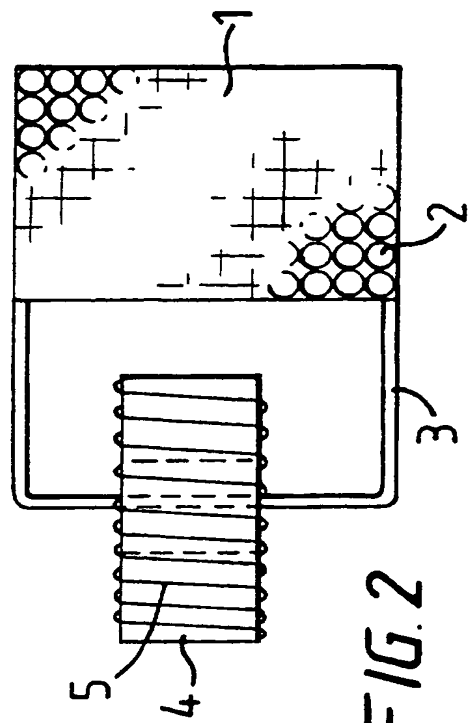

FIG.2

INTERNATIONAL SEARCH REPORT

International Application No
PCT/GB 97/00195

A. CLASSIFICATION OF SUBJECT MATTER
IPC 6 B01L3/00

According to International Patent Classification (IPC) or to both national classification and IPC

B. FIELDS SEARCHED

Minimum documentation searched (classification system followed by classification symbols)
IPC 6 B01L

Documentation searched other than minimum documentation to the extent that such documents are included in the fields searched

Electronic data base consulted during the international search (name of data base and, where practical, search terms used)

C. DOCUMENTS CONSIDERED TO BE RELEVANT

Category °	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
A	EP 0 603 411 A (KATOH KEIICHI ET AL.) 29 June 1994 see column 9, line 45 - column 10, line 14; figures ---	1,7
A	EP 0 058 428 A (EISAI CO LTD) 25 August 1982 see page 6, line 6 - line 22 ---	1,4,7,12
A	US 5 410 130 A (BRAUNSTEIN ZACHARY L) 25 April 1995 see abstract; figures ---	1,7,10
A	WO 95 01559 A (EVOTEC BIOSYSTEMS GMBH ET AL) 12 January 1995 see page 27, last paragraph - page 29, paragraph 1; figures 23-28 -----	1,7

☐ Further documents are listed in the continuation of box C.

☒ Patent family members are listed in annex.

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Date of the actual completion of the international search	Date of mailing of the international search report
7 April 1997	16.04.97

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INTERNATIONAL SEARCH REPORT

Inform[redacted] patent family members

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